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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,694	11/01/2005	Tetsushi Taguchi	052203	7280

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EXAMINER	
GOON, SCARLETT Y	
ART UNIT	PAPER NUMBER
4131	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,694	TAGUCHI ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11 Mar 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a National Stage entry of PCT/JP03/11669 filed on 1 November 2005 and claims priority to foreign application Japan 2002-265982 filed on 11 September 2002. A certified copy of the foreign priority document in Japanese is received.

Claims 1 and 4-11 are pending in the instant application.

Claims 2-3 have been canceled by the Applicants.

Information Disclosure Statement

The information disclosure statement dated 11 March 2005 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 6, 7 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The recitation of a "derivative" in these claims render the claims herein indefinite. The recitations, "low-molecular-weight derivative" and "derivatives thereof," are not clearly defined in the specification. The 10th edition of the Merriam-Webster's Collegiate

Dictionary (Merriam-Webster Incorporated: Springfield, Massachusetts, 1993, pp 311) defines "derivative" as "a chemical substance related structurally to another substance and theoretically derivable from it." Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to "low-molecular-weight derivative" and "derivatives thereof" herein. Thus, it is unclear and indefinite as to how the "derivative" herein is encompassed thereby.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Milewska *et al.* (Milewska *et al.* 1987, J. Prakt. Chem. 61, 8496-8499).

Applicants claim a biological low-molecular-weight derivative obtained by modifying at least one hydroxyl group of a biological low-molecular-weight compound from the citric acid cycle (malic acid, oxaleacetic acid, citric acid, *cis*-aconitic acid and derivatives thereof) with N-hydroxysuccinimide or N-hydroxysulfosuccinimide.

Milewska *et al.* teaches a new method for the synthesis of homoschizokinen and schizokinen. The key intermediate substrate for the synthesis of the target compounds is 2-tert-butyl-1,3-di-N-hydroxysuccinimidyl citrate (p. 449, structure 10), which is prepared from 1,3-dimethyl citrate (p. 449, structure 7).

The key intermediate of 2-tert-butyl-1,3-di-N-hydroxysuccinimidyl citrate disclosed by Milewska *et al.* reads on instant claim 1 because the intermediate is a citric acid derivative (citric acid modified with a tert-butyl group at the 2-position) modified by N-hydroxysuccinimide at the 1- and 3-positions.

Claims 1 and 4-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagura *et al.* (JP 2000-212286, machine translation).

Applicants claim a crosslinked high-molecular-weight product obtained by crosslinking a high-molecular-weight compound with the biological low-molecular-weight derivative. The low-molecular-weight derivative, as claimed in instant claim 1, is a low-molecular-weight compound, selected from the group consisting of malic acid, oxalacetic acid, citric acid and *cis*-aconitic acid, that is reacted with N-hydroxysuccinimide or N-hydroxysulfosuccinimide. The Applicants further claim the high-molecular-weight compound is at least one of proteins, glycosaminoglycans, chitosans, polyamino acids, and polyalcohols. The said glycosaminoglycans comprise chondroitin sulfate, dermatan sulfate, hyaluronic acid, heparin sulfate, heparin and keratin sulfate. The said proteins comprise collagen, atelocollagen, alkali-soluble collagen, gelatin, keratin, serum albumin, egg albumin, hemoglobin, casein, globulin and fibrinogen. The crosslinked high-molecular-weight product can be used to perform crosslinking directly at affected sites or it can be applied after the crosslinking reaction. The crosslinked-high-molecular-weight product comprises a gel that is metabolized in vivo.

Nagura *et al.* discloses a biodegradable gelatin gel (Section 0002) that is obtained by adding a polycarboxylic acid to gelatin and heating it to introduce chemical crosslinkages. Polycarboxylic acids included in the invention are, but not limited to, malonic acid, fumaric acid, succinic acid, adipic acid, citric acid, tartaric acid and malic acid. Nagura *et al.* further teaches that the gel is not limited to crosslinking with gelatin, but also includes water-soluble proteins such as water-soluble polysaccharides (such as chitosan, alginic acid and chondroitin sulfate) and collagen. Nagura *et al.* discloses that the gelatin gel is considered a biodegradable biomaterial that can be used as an artificial skin, wound dressing material, and a cell culture based material (Section 0008).

With respect to the art rejection above, it is noted that Nagura *et al.* does not explicitly indicate that the gelatin gel biomaterial is metabolized in vivo. However, since the gelatin gel claimed by Applicant is the same as that disclosed by Nagura *et al.*, it is inherent that the gelatin gel biomaterial disclosed by Nagura *et al.* can also be metabolized in vivo.

The U.S. Patent Office does not have the facilities for examining and comparing the Applicant's product with the products of the prior art. When, as here, the prior art appears to contain the exact same compound and Applicant's own disclosure supports the suitability of the prior art composition as the inventive compound, the burden is on the Applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

The gelatin gel biomaterial, obtained by heat-induced crosslinkages to polycarboxylic acids, disclosed by Nagura *et al.* reads on instant claims 4-7.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicants claim a crosslinked high-molecular-weight product obtained by crosslinking a high-molecular-weight compound with the biological low-molecular-weight derivative. The low-molecular-weight derivative, is a low-molecular-weight compound, selected from the group consisting of malic acid, oxalacetic acid, citric acid, 2-ketoglutaric acid and *cis*-aconitic acid, that is reacted with N-hydroxysuccinimide or N-hydroxysulfosuccinimide. The Applicants further claim the high-molecular-weight compound is at least one of proteins, glycosaminoglycans, chitosans, polyamino acids, and polyalcohols. The Applicants also claim a method for the synthesis of the biological low-molecular weight derivative, as well as a method for producing a crosslinked high-molecular-weight product. The Applicants further claim the crosslinking of the high-molecular-weight product can be made to occur directly at affected sites and therefore be applied as biological adhesives, hemostatic agents, materials for embolizing blood vessels, and sealing materials for aneurysum. Alternatively, the crosslinked high-molecular-weight product can be applied after the crosslinking reaction, such as when using it as an adhesion preventing agent, scaffold for tissue regeneration, and drug carrier.

Claims 4-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagura *et al.* (JP 2000-212286, machine translation) as applied to claims 4-7, and further in view of US Patent 6,166,130 to Rhee *et al.*

The teachings of Nagura *et al.* are as set forth above in the claim rejections of claims 4-7 under 35 USC § 102. Nagura *et al.* does not teach that the crosslinked high-molecular-weight product can be performed directly at affected sites (as applied to a biological adhesive, a hemostatic agent, a material for embolizing blood vessels and an adhesion preventing agent) or that the high-molecular-weight cross-linked product be formed prior to application (as when applied to an adhesion preventing agent, scaffold for tissue regeneration and drug carrier).

US Patent 6,166,130 to Rhee *et al.* teaches methods for using crosslinked polymer compositions to effect adhesion between a first surface and a second surface. The crosslinked composition can include proteins such as collagen and derivatives of various naturally occurring polysaccharides, such as glycosylaminoglycans (column 11, line 38 and claims 11-13). Rhee *et al.* further teaches methods for using the crosslinked polymer compositions as bioadhesives (abstract and column 17, line 15) to effect tissue augmentation (abstract and line 16), to prevent the formation of surgical adhesions (abstract and column 19, line 53), to coat a surface of a synthetic implant (abstract and column 20, line 20), to treat aneurism (column 20, line 53), and to deliver biologically active agents (column 15, line 32).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nagura *et al.*, concerning the gelatin gel obtained by adding a polycarboxylic acid to gelatin and heating the composition to introduce chemical crosslinkages, with the teachings of Rhee *et al.* (US Patent 6,166,130), regarding methods of using crosslinked polymer compositions in tissue treatment

applications. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Nagura *et al.*, of obtaining a polymer gel film that is both biodegradable and biocompatible for medical applications.

Absent of any evidence to the contrary, and based upon the teachings of the prior art, there would have been reasonable expectation of success to apply a biodegradable gel film to the spectrum of medical applications as discussed by Rhee *et al.*

Claims 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagura *et al.* (JP 2000-212286, machine translation) as applied to claims 4-7, and further in view of US Patent 7,129,209 to Rhee and US Patent 4,757,140 to DeLuca *et al.*

The teachings of Nagura *et al.* are as set forth above in the claim rejections of claims 4-7 under 35 USC § 102. Nagura *et al.* fails to teach a method for producing the biological low-molecular-weight derivative, as well as that of the high-molecular-weight product.

US Patent 7,129,209 to Rhee teaches crosslinked biomaterial compositions which are prepared using hydrophobic polymers as a crosslinking agent. Crosslinked biomaterial compositions are prepared using polyacids (equivalent to the term polycarboxylic acid as used by the Nagura *et al.* reference), chemically derivatized to contain two or more succinimidyl groups (figure 6 described in column 2, line 26 and column 7, line 43), with biomaterials such as collagen and various

glycosylaminoglycans (column 2, line 58). Rhee provides a method for the preparation of crosslinked collagen with disuccinimidyl suberate and bis(sulfosuccinimidyl)suberate in Example 1 (column 11) and Example 3 (column 15). Rhee teaches that there is a general method whereby polyacids can be chemically derivatized to contain two or more succinimidyl groups by reaction with an appropriate molar amount of N-hydroxysuccinimide (NHS) in the presence of N,N'-dicyclohexylcarbodiimide (DCC) (Section 7, line 42). However, Rhee fails to provide specific conditions for the preparation of polyacids chemically derivatized with succinimidyl groups.

US Patent 4,757,140 to DeLuca *et al.* teaches a method for the preparation of N-hydroxysuccinimidyl esters of all-trans- and 13-cis-retinoic acid. DeLuca *et al.* discloses that in the preparation of the N-hydroxysuccinimidyl ester of all-trans-retinoic acid (column 4, line 37), 20 mg of all-trans-retinoic acid (64 μM) in 0.8 mL of dioxane is treated with 7.6 mg of N-hydroxysuccinimide (64 μM) in 0.4 mL of dioxane and 13.6 mg of dicyclohexylcarbodiimide (64 μM) in 0.4 mL of dioxane. The resulting solution is stirred at room temperature for 5 hours and then the product is precipitated.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nagura *et al.*, concerning the gelatin gel obtained by adding a polycarboxylic acid to gelatin and heating the composition to introduce chemical crosslinkages, with the teachings of Rhee (US Patent 7,129,209), which discuss how to prepare crosslinked biomaterial compositions using polyacids chemically derivatized to contain two or more succinimidyl groups with biomaterials such as collagen and various glycosylaminoglycans, with the teachings of DeLuca *et al.*, which

teaches how to prepare N-hydroxysuccinimidyl esters of all-trans- and 13-cis-retinoic acid. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Nagura *et al.*, of obtaining a polymer gel film that is both biodegradable and biocompatible for medical applications.

With regards to the art rejection above, it is noted that DeLuca *et al.* does not specifically recite the reaction conditions of 0.001 - 10% by weight of the acid with 0.001 – 10% by weight of N-hydroxysuccinimide in the presence of 0.001 – 20% by weight of a carbodiimide, as in instant claim 10. Instead, the DeLuca *et al.* reference teaches a reaction wherein the components of acid/N-hydroxysuccinimide/carbodiimide are reacted in a 1:1:1 molar ratio. If a reaction condition was arbitrarily selected (within the limitations of instant claim 11) whereby 10% by weight of citric acid (molecular weight of 192) is reacted with 10% by weight of N-hydroxysulfosuccinimide (molecular weight of 217) in the presence of 10% by weight of N,N'-dicyclohexylcarbodiimide (molecular weight of 206), the resulting molar ratio of all the reagents would be close to 1:1:1, respectively, which reads on the conditions as disclosed by DeLuca *et al.* Moreover, it is considered that one of ordinary skill in the art would find it obvious to vary and/or optimize the ratios of the reactants to provide optimal conditions for the formation of the active ester.

Absent of any evidence to the contrary, and based upon the teachings of the prior art, there would have been reasonable expectation of success in applying the methods of DeLuca *et al.* to prepare N-hydroxysuccinimide esters of polycarboxylic

acids, and crosslink the resulting activated esters with proteins using the methods provided by Rhee, to form the biodegradable gelatin gel described by Nagura *et al.*

Conclusion

Claims 1 and 4-11 are rejected.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent 5,752,974 to Rhee *et al.* discloses a method for completely or partially blocking, augmenting, sealing, or filling various biological lumens and voids within the body of a patient with crosslinked biomaterial.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Cecilia Tsang can be reached on 571-272-0562 and Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JANET L ANDRES/
Supervisory Patent Examiner, Art Unit 4131

/S. G./
Examiner, Art Unit 4131